PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 18 May 2000 (18.05.00)	
International application No. PCT/GB99/03180	**Applicant's or agent's file reference** N75353A
International filing date (day/month/year) 22 September 1999 (22.09.99)	**Priority date** (day/month/year) 22 September 1998 (22.09.98)
Applicant WILSON, Robert, John, Macleod et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

20 April 2000 (20.04.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

REC'D 17 NOV 2000
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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
N75353A		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/03180	22/09/1999	22/09/1998
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant MEDICAL RESEARCH COUNCIL et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/04/2000	15.11.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fayos, C Telephone No. +49 89 2399 2180

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03180

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-27 as originally filed

Claims, No.:

1-13 as received on 26/09/2000 with letter of 19/09/2000

Drawings, sheets:

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-3 and 7-11 (all partially) and clams 12-13 (industrial applicability).

because:

☒ the said international application, or the said claims Nos. 12-13 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-3 and 7-11 (all partially) are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-13

	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-6 and 9-13
	No:	Claims	7-8
Industrial applicability (IA)	Yes:	Claims	1-8 and 10-11; claims 9 and 12-13 see separate sheet
	No:	Claims	-

2. Citations and explanations
see separate sheet

Re Item I

Basis of the opinion

1- Sequence listing pages 1-8 have been taken into account (Rule 13 PCT).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

2- Claims 9 and 12-13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

3- As indicated in the international search report (see PCT/ISA/210), the search has been limited to those parts of the claims which appear to be clear, supported and disclosed, namely, those parts relating to the compounds being antibodies to the ycf 24 product and antisense inhibitors capable of hybridizing with the ycf 24 mRNA (see description of the present application p 11 lines 25-30 and p 12 lines 6-11) as well as to the inventive concept towards which the claims are directed, so that only claims 4-6 have been searched completely.

According to Rule 66.1(e) PCT, no international preliminary examination will be carried out with regards to the subject matter which is not covered by the search report (i. e. claims 1-3 and 7-13 all partially).

3.1- Thus, for the purpose of this opinion, the feature "an inhibitor of ycf 24 gene product expression and/or activity" has been read as if it was restricted to antibodies to the ycf 24 product and antisense inhibitors capable of hybridizing with the ycf 24 mRNA (see description of the present application p 11 lines 25-30 and p 12 lines 6-11).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

4- Reference is made to the following documents:

D1: MCCONKEY G.A. ET AL: 'Inhibition of Plasmodium falciparum protein synthesis' THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 4, 1997, pages 2046-2049, XP002135059

D2: WO 98 35057 A (KARA ANNA KATE URSULA ;NELSON JAMES STUART (SG); UNIV SINGAPORE (S) 13 August 1998 (1998-08-13)

D3: DATABASE EMBL [Online] ACCESION NUMBER X95275, 29 June 1996 (1996-06-29) WILSON R.J.M. ET AL: 'Complete gene map of the plastid-like DNA of the malaria parasite Plasmodium falciparum' XP002135064 -& J.MOL.BIOL. 261:155-172 (1996) XP000891792

D4: DATABASE EMBL [Online] ACCESION NUMBER D64004, 4 October 1995 (1995-10-04) KANEKO T. ET AL: 'Sequence analysis of the genome of the unicellular Cyanobacterium Synechocystis sp. strain PCC6803. I. Sequence features in the 1 Mb region from map positions 64% to 92% of the genome' XP002135065 -& DNA RESEARCH 2, 153-166 (1995) XP000891791

D5: DATABASE EMBL [Online] ACCESION NUMBER AE000263, BLATTNER F.R. ET AL: 'THE COMPLETE GENOME SEQUENCE OF ESCHERICHIA COLI K-12' XP002135066 -& SCIENCE 277, 1997, 1453-1474 XP002135063

D6: DENNY ET AL.: Evidence for a single origin of the 35 kb plastid DNA in Apicomplexans. Protist Vol. 159, 51-59, February 1998.

NOVELTY - Art. 33 (1) and (2) PCT

5- Claims 1-13 appear to be novel in the light of the prior art cited in the search report (provided the restriction mentioned in item III 3-).

5.1- None of the prior art documents cited in the search report explicitly discloses antibodies to the ycf24 gene product and antisense inhibitors capable of hybridising

with ycf24 mRNA (see item III 3-), the use of said antibodies to the ycf24 gene product and antisense inhibitors capable of hybridising with ycf24 mRNA (see item III 3-) in a method of treatment of the human or animal body by therapy, for inhibiting the growth of an organism which comprises the ycf24, or a method of identifying a compound that inhibits the growth of an organism comprising the *ycf 24* gene

5.2- The subject matter of claims 1-13 (provided the restrictions mentioned in Item III 3-) is considered as being novel over the prior art cited in the search report.

INVENTIVE STEP - Art. 33 (1) and (3) PCT

6- **Claims 7 and 8 lack inventive step and claims 1-6 and 9-13 appear to be inventive (provided the restrictions mentioned in Item III 3-) in the light of the available prior art:**

6.1- The problem posed in the present application is to provide means for inhibiting growth of and/or treating infection by organisms which comprise the *ycf 24* gene.

The solution proposed in the present application is the use of an antibody to the ycf24 gene product and/or antisense inhibitor capable of hybridising with ycf24 mRNA (see restrictions Item III 3-).

6.2- D1 discloses the use of **thiostrepton** to inhibit growth of P. falciparum (malaria parasite). D1 demonstrates a selective effect of thiostrepton on organelle function that is suggestive of interference in the protein synthesis apparatus of the plastid. Sensitivity of P. falciparum to thiostrepton confirms that **the plastid-like genome is essential for the erythrocytic cycle** and presents a novel therapeutic site for this class of antibiotics (Abstract). Furthermore, although the function of the 35 kb plastid like organelle is not known, inhibition of growth by thiostrepton indicates that protein synthesis from this organelle is **essential for growth of the blood stages of the parasite and hence, protein synthesis derived from the plastid like genome may be a general target for antibiotics in animal and human parasites** (p 2049

c 1 § 1 and 2).

D2 shows that **thiostrepton inhibits growth of blood-stage cultures of the malaria parasite P. falciparum**, probably by inhibiting protein synthesis in the unusual plastid-like organelle of the parasite, the target for thiostrepton in P. falciparum being presumably plastid encoded protein synthesis (p 715 c 1 § 1 and 2).

6.3- Thus, D1 and D2 provide means for inhibiting growth of and/or treating infection by organisms which comprise a plastid-like genome (by inhibiting protein synthesis in the plastid-like organelle) and are considered to be the closest prior art.

6.4- D3 demonstrates that blocking replication of the 35 kb circular DNA that comprises the plastid genome in T. gondii is lethal (Abstract - p 408 c 1 § 1-2).

D4 mentions the further use of polypeptides encoded by the extrachromosomal plastid like element and their homologues, analogues and derivatives, as targets for drug design and in the development of anti-malarial vaccines (p 11 lines 6-9).

D5 discloses the complete gene map of the plastid like DNA of the malaria parasite Plasmodium falciparum and mentions a highly conserved ORF (ORF 470, i. e. *ycf 24* gene) of unknown function found in bacteria and "primitive" red algal plastids.

6.5- The ycf 24 gene (ORF 470) is known and its DNA sequence has been disclosed (see e. g. D5). The manufacture of antibodies to the ycf 24 product and antisense inhibitors capable of hybridizing with the ycf 24 mRNA are merely part of routine experimental procedures, that the person skilled in the art would carry out, without the exercise of inventive skill, in accordance with the circumstances, when confronted to a new gene of interest.

The compounds of claims 7 and 8 (see restriction Item III 3-) cannot be considered as being inventive in the light of e. g. D5, and claims 7 and 8 lack therefore inventive

step.

6.7- However, there are some technical reasons to consider that the sole high conservation of the *ycf 24* gene (ORF 470) is not enough to acknowledge the fact that said gene is essential for the growth of organism comprising said gene or that the inhibition of the expression or activity of the *ycf 24* gene would provide an effective way of inhibiting the growth of organism comprising said gene, i. e. :

- *ycf 24* gene could have functioned in a redundant pathway, i. e. loss of the gene encoding *ycf 24* may not have been lethal because organisms could have survives without the gene.

- The malaria plastid encodes other proteins, such as a protein called CLpC which is a potential chaperone proposed to be involved in the import of proteins into the organelle (an essential process). The essential nature of protein synthesis by the malaria plastid may have arisen from the requirement for such other proteins, not for *ycf 24*.

- *ycf 24*'s primary function might have been in the mosquito rather than the vertebrate part of the malarial life cycle. This would have made it an unattractive target for inhibition by drugs because such inhibition would have had no effect on clearing the parasite from the vertebrate host.

- *ycf 24*'s function might have also been encoded by another protein encoded in the nucleus. Thus, *ycf 24*'s function may have been redundant over a protein encoded in the nucleus.

It was therefore not obvious that the *ycf 24* protein was essential and that the use of an antibody to the ycf24 gene product and/or antisense inhibitor capable of hybridising with ycf24 mRNA (see restrictions Item III 3-) would inhibit growth of and/or treat infection by organisms which comprise the *ycf 24* gene.

6.8- Therefore, in the light of the prior art cited in the search report and of the

observations made in item 6.7- above, claims 1-6 and 9-13 can be considered as being inventive (provided the restrictions mentioned in Item III 3-).

INDUSTRIAL APPLICABILITY - Art. 33 (1) and (4) PCT

6- For the assessment of the present claims 9 and 12-13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

6.1- Claims 1-8 and 10-11 (see restriction Item III 3-) appear to be industrially applicable and as such meet the requirements of Art. 33 (1) and (4) PCT.

Claims

1. An inhibitor of *ycf 24* gene product expression and/or activity for use in a method of treatment of infection of the human or animal body by an organism comprising said gene.

2. An inhibitor according to claim 1 for use in a method of treatment of malaria.

3. A method of inhibiting the growth of an organism comprising the *ycf 24* gene, which method comprises contacting the organism ex vivo with an inhibitor of expression and/or activity of the gene product.

4. A method of identifying a compound that inhibits the growth of an organism comprising the *ycf 24* gene, the method comprising
(i) contacting a test compound with the *ycf 24* gene product, and
(ii) determining whether the test compound inhibits the activity of or binds to the product, any such binding or inhibition being indicative that the compound inhibits the growth of the organism.

5. A method of identifying a compound that inhibits the growth of an organism comprising the *ycf 24* gene, the method comprising
(i) contacting a test compound with a test construct comprising a *ycf 24* promoter operably linked to a coding sequence,
(ii) determining whether the test compound inhibits expression driven by the promoter, any such inhibition being indicative that the compound inhibits the growth of the organism.

6. A method according to claim 4 or 5 in which the organism is a malaria parasite.

7. A compound identified by the method of any one of claims 4 to 6.

8. A compound according to claim 7 for use in the prevention or treatment of an infection by an organism comprising the *ycf 24* gene.

9. A method of inhibiting the growth of an organism comprising the *ycf 24* gene, said method comprising contacting the organism ex vivo with a compound according to claim 7.

10. Use of a compound according to claim 7 for the manufacture of a medicament for the treatment of an infection by an organism comprising the *ycf 24* gene.

11. A pharmaceutical composition comprising an inhibitor of *ycf 24* gene product expression and/or activity or a compound as defined in claim 7 and a pharmaceutically acceptable carrier or diluent.

12. A method of preventing or treating infection by a unicellular organism comprising the *ycf 24* gene in a patient, said method comprising administering to the patient an inhibitor of *ycf 24* gene product expression and/or activity or a compound as defined in claim 7.

13. A method according to claim 12 in which the organism is a malaria parasite.

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PATENT COOPERATION TREATY

REC'D 05 DEC 2000

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
N75353A		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/03180	22/09/1999	22/09/1998
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant MEDICAL RESEARCH COUNCIL et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

CORRECTED VERSION

Date of submission of the demand	Date of completion of this report
20/04/2000	01.12.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fayos, C Telephone No. +49 89 2399 2180

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03180

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-27 as originally filed

Claims, No.:

1-11 with telefax of 24/11/2000

Drawings, sheets:

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-3 and 7-9 (all partially) and claims 10-11 (Industrial Applicability).

because:

☒ the said international application, or the said claims Nos. 10-11 (Industrial Applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-3 and 7-9 (all partially) are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-11

	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-11
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-9; 10-11 see separate sheet
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item I

Basis of the opinion

1- Sequence listing pages 1-8 have been taken into account (Rule 13 PCT).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

2- Claims 10-11 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

3- As indicated in the international search report (see PCT/ISA/210), the search has been limited to those parts of the claims which appear to be clear, supported and disclosed, namely, those parts relating to the compounds being antibodies to the ycf 24 product and antisense inhibitors capable of hybridizing with the ycf 24 mRNA (see description of the present application p 11 lines 25-30 and p 12 lines 6-11) as well as to the inventive concept towards which the claims are directed, so that only claims 4-6 have been searched completely.

According to Rule 66.1(e) PCT, no international preliminary examination will be carried out with regards to the subject matter which is not covered by the search report (i. e. claims 1-3 and 7-11 all partially).

3.1- Thus, for the purpose of this opinion, the feature "an inhibitor of ycf 24 gene product expression and/or activity" has been read as if it was restricted to antibodies to the ycf 24 product and antisense inhibitors capable of hybridizing with the ycf 24 mRNA (see description of the present application p 11 lines 25-30 and p 12 lines 6-11).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

4- Reference is made to the following documents:

D1: MCCONKEY G.A. ET AL: 'Inhibition of Plasmodium falciparum protein synthesis' THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 4, 1997, pages 2046-2049, XP002135059

D2: WO 98 35057 A (KARA ANNA KATE URSULA ;NELSON JAMES STUART (SG); UNIV SINGAPORE (S) 13 August 1998 (1998-08-13)

D3: DATABASE EMBL [Online] ACCESION NUMBER X95275, 29 June 1996 (1996-06-29) WILSON R.J.M. ET AL: 'Complete gene map of the plastid-like DNA of the malaria parasite Plasmodium falciparum' XP002135064 -& J.MOL.BIOL. 261:155-172 (1996) XP000891792

D4: DATABASE EMBL [Online] ACCESION NUMBER D64004, 4 October 1995 (1995-10-04) KANEKO T. ET AL: 'Sequence analysis of the genome of the unicellular Cyanobacterium Synechocystis sp. strain PCC6803. I. Sequence features in the 1 Mb region from map positions 64% to 92% of the genome' XP002135065 -& DNA RESEARCH 2, 153-166 (1995) XP000891791

D5: DATABASE EMBL [Online] ACCESION NUMBER AE000263, BLATTNER F.R. ET AL: 'THE COMPLETE GENOME SEQUENCE OF ESCHERICHIA COLI K-12' XP002135066 -& SCIENCE 277, 1997, 1453-1474 XP002135063

D6: DENNY ET AL.: Evidence for a single origin of the 35 kb plastid DNA in Apicomplexans. Protist Vol. 159, 51-59, February 1998.

NOVELTY - Art. 33 (1) and (2) PCT

5- Claims 1-11 appear to be novel in the light of the prior art cited in the search report (provided the restriction mentioned in item III 3-).

5.1- None of the prior art documents cited in the search report explicitly discloses antibodies to the ycf24 gene product and antisense inhibitors capable of hybridising

with ycf24 mRNA (see item III 3-), the use of said antibodies to the ycf24 gene product and antisense inhibitors capable of hybridising with ycf24 mRNA (see item III 3-) in a method of treatment of the human or animal body by therapy, for inhibiting the growth of an organism which comprises the ycf24, or a method of identifying a compound that inhibits the growth of an organism comprising the *ycf 24* gene

5.2- The subject matter of claims 1-11 (provided the restrictions mentioned in Item III 3-) is considered as being novel over the prior art cited in the search report.

INVENTIVE STEP - Art. 33 (1) and (3) PCT

6- Claims 1-11 appear to be inventive (provided the restrictions mentioned in Item III 3-) in the light of the available prior art:

6.1- The problem posed in the present application is to provide means for inhibiting growth of and/or treating infection by organisms which comprise the *ycf 24* gene.

The solution proposed in the present application is the use of an antibody to the ycf24 gene product and/or antisense inhibitor capable of hybridising with ycf24 mRNA (see restrictions Item III 3-).

6.2- D1 discloses the use of **thiostrepton** to inhibit growth of P. falciparum (malaria parasite). D1 demonstrates a selective effect of thiostrepton on organelle function that is suggestive of interference in the protein synthesis apparatus of the plastid. Sensitivity of P. falciparum to thiostrepton confirms that **the plastid-like genome is essential for the erythrocytic cycle** and presents a novel therapeutic site for this class of antibiotics (Abstract). Furthermore, although the function of the 35 kb plastid like organelle is not known, inhibition of growth by thiostrepton indicates that protein synthesis from this organelle is **essential for growth of the blood stages of the parasite and hence, protein synthesis derived from the plastid like genome may be a general target for antibiotics in animal and human parasites** (p 2049 c 1 § 1 and 2).

D2 shows that **thiostrepton inhibits growth of blood-stage cultures of the malaria parasite P. falciparum**, probably by inhibiting protein synthesis in the unusual plastid-like organelle of the parasite, the target for thiostrepton in P. falciparum being presumably plastid encoded protein synthesis (p 715 c 1 § 1 and 2).

6.3- Thus, D1 and D2 provide means for inhibiting growth of and/or treating infection by organisms which comprise a plastid-like genome (by inhibiting protein synthesis in the plastid-like organelle) and are considered to be the closest prior art.

6.4- D3 demonstrates that blocking replication of the 35 kb circular DNA that comprises the plastid genome in T. gondii is lethal (Abstract - p 408 c 1 § 1-2).

D4 mentions the further use of polypeptides encoded by the extrachromosomal plastid like element and their homologues, analogues and derivatives, as targets for drug design and in the development of anti-malarial vaccines (p 11 lines 6-9).

D5 discloses the complete gene map of the plastid like DNA of the malaria parasite Plasmodium falciparum and mentions a highly conserved ORF (ORF 470, i. e. *ycf 24* gene) of unknown function found in bacteria and "primitive" red algal plastids.

6.5- However, there are some technical reasons to consider that the sole high conservation of the *ycf 24* gene (ORF 470) is not enough to acknowledge the fact that said gene is essential for the growth of organism comprising said gene or that the inhibition of the expression or activity of the *ycf 24* gene would provide an effective way of inhibiting the growth of organism comprising said gene, i. e. :

- *ycf 24* gene could have functioned in a redundant pathway, i. e. loss of the gene encoding *ycf 24* may not have been lethal because organisms could have survives without the gene.

- The malaria plastid encodes other proteins, such as a protein called CLpC

which is a potential chaperone proposed to be involved in the import of proteins into the organelle (an essential process). The essential nature of protein synthesis by the malaria plastid may have arisen from the requirement for such other proteins, not for *ycf 24*.

- *ycf 24*'s primary function might have been in the mosquito rather than the vertebrate part of the malarial life cycle. This would have made it an unattractive target for inhibition by drugs because such inhibition would have had no effect on clearing the parasite from the vertebrate host.

- *ycf 24*'s function might have also been encoded by another protein encoded in the nucleus. Thus, *ycf 24*'s function may have been redundant over a protein encoded in the nucleus.

It was therefore not obvious that the *ycf 24* protein was essential and that the use of an antibody to the ycf24 gene product and/or antisense inhibitor capable of hybridising with ycf24 mRNA (see restrictions Item III 3-) would inhibit growth of and/or treat infection by organisms which comprise the *ycf 24* gene.

6.6- Therefore, in the light of the prior art cited in the search report and of the observations made in item 6.5- above, claims 1-11 can be considered as being inventive (provided the restrictions mentioned in Item III 3-).

INDUSTRIAL APPLICABILITY - Art. 33 (1) and (4) PCT

6- For the assessment of the present claims 10-11 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound

for the manufacture of a medicament for a new medical treatment.

6.1- Claims 1-9 (see restriction Item III 3-) appear to be industrially applicable and as such meet the requirements of Art. 33 (1) and (4) PCT.

Claims

1. An inhibitor of *ycf 24* gene product expression and/or activity for use in a method of treatment of the human or animal body by therapy.

2. An inhibitor according to claim 1 for use in a method of treatment of infection by an organism.

3. An inhibitor according to claim 2 for use in a method of treatment of malaria.

4. A method of inhibiting the growth of an organism comprising contacting the organism ex vivo with an inhibitor of *ycf 24* gene product expression and/or activity.

5. A method of identifying a compound that inhibits the growth of an organism comprising
(i) contacting a test compound with the *ycf 24* gene product, and
(ii) determining whether the test compound inhibits the activity of or binds to the product, any such binding or inhibition being indicative that the compound inhibits the growth of the organism.

6. A method of identifying a compound that inhibits the growth of an organism comprising
(i) contacting a test compound with a test construct comprising a *ycf 24* promoter operably linked to a coding sequence,
(ii) determining whether the test compound inhibits expression driven by the promoter, any such inhibition being indicative that the compound inhibits the growth of the organism.

7. A method according to claim 5 or 6 in which the organism is a malaria parasite.

8. A compound identified by the method of any one of claims 5 to 7.

9. A compound according to claim 8 for use in the prevention or treatment of an infection by an organism.

10. A method of inhibiting the growth of an organism comprising contacting the organism ex vivo with a compound according to claim 8.

11. Use of a compound according to claim 8 for the manufacture of a medicament for the treatment of an infection by an organism.

12. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 3 or 8 and a pharmaceutically acceptable carrier or diluent.

13. A method of treating preventing or treating infection by a unicellular organism in a patient comprising administering to the patient an inhibitor as defined in any one of claims 1 to 3 or 8.

14. A method according to claim 13 in which the organism is a malaria parasite.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 31/00, 38/00, G01N 33/50, A61P 31/00, A61K 33/06 // 39/395, 31/7088

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(71) Applicant (*for all designated States except US*): MEDICAL RESEARCH COUNCIL [GB/GB]; 20 Park Crescent, London W1N 4AL (GB).

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: TREATMENT OF INFECTION

(57) Abstract

An inhibitor of *ycf 24* gene product expression and/or activity is used in a method of treatment of the human or animal body by therapy. In particular the inhibitor is used in a method of treatment of infection by an organism. The organism may be a malaria parasite, such as *Plasmodium falciparum*. The invention also provides a method of inhibiting the growth of an organism comprising contacting the organism ex vivo with an inhibitor of *ycf 24* gene product expression and/or activity. The invention further provides a method of identifying a compound that inhibits the growth of an organism comprising (i) contacting a test compound with the *ycf 24* gene product, and (ii) determining whether the test compound inhibits the activity of or binds to the product, any such binding or inhibition being indicative that the compound inhibits the growth of the organism.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/00, 38/00, G01N 33/50, A61P 31/00, 33/06 // A61K 39/395, 31/7088

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(71) Applicant *(for all designated States except US)*: MEDICAL RESEARCH COUNCIL [GB/GB]; 20 Park Crescent, London W1N 4AL (GB).

(72) Inventors; and
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(74) Agent: CAMPBELL, Patrick, John, Henry; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5LX (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: TREATMENT OF INFECTION

(57) Abstract

An inhibitor of *ycf 24* gene product expression and/or activity is used in a method of treatment of the human or animal body by therapy. In particular the inhibitor is used in a method of treatment of infection by an organism. The organism may be a malaria parasite, such as *Plasmodium falciparum*. The invention also provides a method of inhibiting the growth of an organism comprising contacting the organism ex vivo with an inhibitor of *ycf 24* gene product expression and/or activity. The invention further provides a method of identifying a compound that inhibits the growth of an organism comprising (i) contacting a test compound with the *ycf 24* gene product, and (ii) determining whether the test compound inhibits the activity of or binds to the product, any such binding or inhibition being indicative that the compound inhibits the growth of the organism.

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INTERNATIONAL SEARCH REPORT

[redacted] ial Application No
PCT/GB 99/03180

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/00 A61K38/00 G01N33/50 A61P31/00 A61P33/06
//A61K39/395,A61K31/7088

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MCCONKEY G.A. ET AL: "Inhibition of Plasmodium falciparum protein synthesis" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 4, 1997, pages 2046-2049, XP002135059 abstract	1-4,8-14
X	ROGERS M.J. ET AL: "The antibiotic micrococcin is a potent inhibitor of growth and protein synthesis in the malaria parasite" ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 42, no. 3, March 1998 (1998-03), pages 715-716, XP000891786 abstract	1-4,8-14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
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Date of the actual completion of the international search	Date of mailing of the international search report
7 April 2000	03/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fernandez y Branas,F

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	FICHERA M.E. ET AL: "A plastid organelle as a drug target in apicomplexan parasites" NATURE, vol. 390, 1997, pages 407-409, XP002135060 abstract	1,2,4, 8-13
A	WO 98 35057 A (KARA ANNA KATE URSULA ;NELSON JAMES STUART (SG); UNIV SINGAPORE (S) 13 August 1998 (1998-08-13) pages 54-59, SEQ ID No 1 page 11, line 6 - line 9	1-14
A	DATABASE EMBL 'Online! ACCESION NUMBER X95275, 29 June 1996 (1996-06-29) WILSON R.J.M. ET AL: "Complete gene map of the plastid-like DNA of the malaria parasite Plasmodium falciparum" XP002135064 abstract -& J.MOL.BIOL. 261:155-172 (1996) XP000891792	1-14
A	DATABASE EMBL 'Online! ACCESION NUMBER D64004, 4 October 1995 (1995-10-04) KANEKO T. ET AL: "Sequence analysis of the genome of the unicellular Cyanobacterium Synechocystis sp. strain PCC6803. I. Sequence features in the 1 Mb region from map positions 64% to 92% of the genome" XP002135065 abstract -& DNA RESEARCH 2, 153-166 (1995) XP000891791	1-14
A	DATABASE EMBL 'Online! ACCESION NUMBER AE000263, BLATTNER F.R. ET AL: "THE COMPLETE GENOME SEQUENCE OF ESCHERICHIA COLI K-12" XP002135066 abstract -& SCIENCE 277, 1997, 1453-1474 XP002135063	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/03180

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 13-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

Claims: 1-4, 8-14 (all partially)

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4, 8-14 (all partially)

Present claims 1-4 and 8-14 relate to compounds defined by reference to a desirable characteristic or property, namely the capability to inhibit the ycf 24 gene product expression and/or activity.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds being antibodies to the ycf 24 product and antisense inhibitors capable of hybridising with ycf 24 mRNA, see description page 11 lines 25-30 and page 12 lines 6-11, as well as to the inventive concept towards which the claims are directed.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

[redacted]ation on patent family members

[redacted]al Application No
PCT/GB 99/03180

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9835057 A	13-08-1998	AU 5777798 A	26-08-1998